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The shape and free energy of a lipid bilayer surrounding a membrane inclusion

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ABSTRACT

Membrane inclusion interactions are studied within the scope of continuum theory. We show that the free energy functional for the membrane thickness can be rewritten as a constant times a dimensionless integral. For cylindrical inclusions, the resulting differential equation gives a thickness profile that depends on the radius of the cylinder and one single lipid property, a correlation length that is determined by the ratio of the thickness compressibility and bending moduli. The solutions decay in a non-monotonic fashion with one single observable minimum. A solution for planar geometry may either be explicitly constructed or obtained by letting the radius of the cylinder go to infinity. In dimensionless units the initial derivative of the thickness profile is universal and equal to $-1/\sqrt{2}$. In physical units, the derivative depends on the size of the hydrophobic mismatch as well as the membrane correlation length and will usually be fairly small but clearly non-zero. The line tension between the protein inclusion and a fluid phase membrane will depend on the hydrophobic mismatch and be of the order of 10 pN (larger for the gel phase). This results in free energy costs for the inclusion that will be up to tens of kJ/mol (in the fluid phase).

1. Introduction

A membrane protein with hydrophobic thickness that is different from the surrounding lipid bilayer will induce a strain upon the lipids. This was noticed and formulated in the mattress model (Mouritsen and Bloom, 1984). Aranda-Espinoza et al. (1996) have showed that an analytical solution to the inclusion problem exists and West et al. (2009) have employed this theory as well as Landau-de Gennes theory to analyze results from recent coarse grained simulations (West et al., 2009). Also an extended theory based on Aranda-Espinoza et al. (1996), that includes all known elastic terms of the membrane and capture thermal fluctuations of the bilayer fairly accurate, has been proposed by Brannigan and Brown (2006).

With the advance of computer simulation methods this can be probed by calculating the shape and extension of the perturbation upon the surrounding bilayer. This has been reported by several authors (Johansson and Edholm, 1987; Sperotto and Mouritsen, 1991; Venturoli et al., 2005; Cordomi and Perez, 2007). A perturbation that extends about 1–2 nm from the protein has been observed in these cases. This perturbation has often been fitted to an exponential function which usually has been successful within the statistical accuracy of the simulations. Cordomi and Perez (2007) observes, however in one case that the decay might be better described as a damped oscillation.

For hydrophobic inclusions with heights much larger than the equilibrium thickness of the membrane one also needs to consider a tilt scenario where the hydrophobic mismatch drives a rotation of the inclusion. This effect has been observed in simulation studies of protein membrane interactions (Kim and Im, 2010). For large mismatches, the exposure of hydrophobic matter to water may also be an alternative. This will be discussed later in the present article. For the moment, we just note that a hydrophobic mismatch of 1 nm would by exposing hydrophobic area to water give rise to a line tension of 50 pN corresponding to a free energy of 200 kJ/mol for a cylindrical protein with radius 1 nm. We will here show that these number can be substantially reduced by deforming the membrane instead of exposing hydrophobic area. Finally, effects that go beyond continuum theory like hydrogen bonding may change the suggested picture.

We will here show that a damped oscillation, not a pure exponential decay is the outcome of a simple continuum model for the membrane. Since our assumptions about the membrane inclusion is different compared to previous work (Aranda-Espinoza et al., 1996; Brannigan and Brown, 2006) we also show that the inclusion problem can be formulated as a variational problem for a dimensionless integral. Free energies and line tension are also derived from the model.

The free energy cost for introducing the inclusion into the bilayer may in a continuum approximation be written (Lindahl and Edholm, 2000) as an integral over the spatially varying free energy

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cost to change the membrane thickness in order to adapt the membrane to the protein. This may be written as an integral over the first non-vanishing terms of an expansion in bilayer thickness and its derivatives

$$F[t] = \frac{1}{2}\int\int [k_e|t - t_0|^2 + \gamma|\nabla t|^2 + k_d|\nabla^2 t|^2]dxdy. \quad (1)$$

Here $t(x, y)$ is the bilayer thickness at the point (x, y) and t_0 the preferred equilibrium thickness of the membrane. The first term, describes the energetic cost to deviate from this preferred thickness. The second term is a surface tension term, which describes the cost of free energy to change the surface area of the system due to a spatially varying thickness. The coefficient γ is the surface tension (coefficient), that will be zero in a system which is free to adjust its area and not subject to strain. The third term describes the cost of free energy to have a curvature (non-linear variation) of the bilayer thickness and is similar to the bending energy of the bilayer but with the requirement that the bending of the two monolayers is anti-correlated not correlated.

2. Theory

We assume that the inclusion (protein) is free to adjust its center in the normal direction of the membrane. It will then minimize the free energy cost for insertion by aligning its hydrophobic center with the membrane mid-plane. We introduce therefore $h = t/2$, $h_0 = t_0/2$ and the hydrophobic thickness of the inclusion, $2h_1$. We define a lateral membrane length scale

$$\xi = \left[\frac{k_d}{k_e}\right]^{1/4} \quad (2)$$

and the dimensionless coordinates

$$\boldsymbol{\rho} = \mathbf{r}/\xi = (x, y)/\xi = \rho(\cos\varphi, \sin\varphi). \quad (3)$$

As normalized membrane (half) thickness, we introduce

$$f(\boldsymbol{\rho}) = \frac{h(\boldsymbol{\rho}) - h_0}{h_1 - h_0}, \quad (4)$$

which will be 0 for an unstrained bilayer and 1 for a bilayer that perfectly matches the hydrophobic thickness of the inclusion. In terms of these variables, Eq. (1) may be written

$$F[f(\boldsymbol{\rho})] = 2F_0\int\int [f^2 + \gamma_0|\nabla f|^2 + |\nabla^2 f|^2]\rho d\rho d\varphi, \quad (5)$$

with the constant in front of the dimensionless integral, F_0, being $\gamma_1(h_1 - h_0)^2$, where $\gamma_1 \equiv \sqrt{k_d k_e}$ is another force constant of the membrane. It has the dimension of a surface tension (but is of course not a surface tension). We have also introduced the dimensionless surface tension $\gamma_0 = \gamma/\gamma_1$. Typical values for the membrane material constants give the correlation length $\xi = 1-2$ nm while F_0 being quadratic in the mismatch will be 6 kJ/mol for a 30% mismatch. For general shapes of the inclusion, the further analysis becomes complicated. We therefore specialize to a cylindrical inclusion with radius R. This gives

$$F[f(\rho)] = 4\pi F_0\int_{R/\xi}^{\infty}\left[f^2 + \gamma_0\left(\frac{df}{d\rho}\right)^2 + \left(\frac{1}{\rho}\frac{d}{d\rho}\rho\frac{d}{d\rho}f\right)^2\right]\rho d\rho. \quad (6)$$

The function $f(\rho)$ that describes the shape of the membrane around the inclusion is found by minimizing this functional subject to the proper boundary conditions at $\rho = R/\xi$. $f(\rho)$obeys the Euler–Lagrange equation which in this case becomes

$$\rho^4\frac{d^4f(\rho)}{d\rho^4} + 2\rho^3\frac{d^3f(\rho)}{d\rho^3} - (1 - \gamma_0\rho^2)\left(\rho^2\frac{d^2f(\rho)}{d\rho^2} - \rho\frac{df(\rho)}{d\rho}\right) + \rho^4 f(\rho) = 0. \quad (7)$$

We now specialize to a bilayer with surface tension zero. The differential equation may then be written as

$$\left(\frac{d^2}{d\rho^2} + \frac{1}{\rho}\frac{d}{d\rho} - i\right)\left(\frac{d^2}{d\rho^2} + \frac{1}{\rho}\frac{d}{d\rho} + i\right)f(\rho) = 0. \quad (8)$$

This is a homogeneous ordinary differential equation with variable coefficients that has Bessel functions of imaginary arguments as solutions. They are $J_0(\rho e^{\pi i/4})$ and $K_0(\rho e^{\pi i/4})$, where J_0 is the ordinary Bessel function of zeroth order and the K_0 is the zeroth order modified Bessel function of the second kind. Alternatively, the solution may be expressed in terms of the four real valued Kelvin functions (Abramowitz and Stegun, 1968)

$$f(\rho) = a_0\mathrm{ber}_0(\rho) + a_1\mathrm{bei}_0(\rho) + a_2\mathrm{ker}_0(\rho) + a_3\mathrm{kei}_0(\rho). \quad (9)$$

We seek solutions that are bounded in the membrane region and have therefore to put the coefficients, a_0 and a_1 in front of the exponentially increasing ber and bei solutions to zero. The boundary conditions for f and f' at $\rho = R/\xi$, determines the other two constants, a_2 and a_3. By introducing the boundary conditions as:

$$f(R/\xi) = \psi \quad \text{and} \quad f'(R/\xi) = \psi', \quad (10)$$

we may express the constants as

$$a_0 = 0, \quad a_1 = 0, \quad a_2 = \frac{\psi\hat{k}' - \psi'\hat{k}}{N}, \quad a_3 = \frac{\psi' k - \psi k'}{N} \quad (11)$$

with $\hat{k} \equiv \mathrm{kei}_0(R/\xi)$ and $k \equiv \mathrm{ker}_0(R/\xi)$ and $N \equiv \mathrm{kei}_0'(R/\xi)\mathrm{ker}_0(R/\xi) - \mathrm{kei}_0(R/\xi)\mathrm{ker}_0'(R/\xi)$.

2.1. Rigid protein description

For a rigid cylindrical protein, using the dimensionless variables, we have immediately one of the boundary conditions $f(R/\xi) = \psi = 1$ while the initial derivative $f'(R/\xi) = \psi'$ has to be determined by minimizing the free energy. By inserting the solution from Eq. (9) with the constants from Eq. (11) ($\psi = 1$) into Eq. (6) straightforward calculations give the free energy as a function of the initial derivative, ψ' as

$$F(\psi') = \frac{4\pi F_0}{N^2}((\psi' k - k')^2 + (\hat{k}' - \psi'\hat{k})^2)\int_{R/\xi}^{\infty}\left[\mathrm{kei}_0^2(\rho) + \mathrm{ker}_0^2(\rho)\right]\rho d\rho. \quad (12)$$

Minimizing the free energy with respect to ψ' gives

$$\psi' = \frac{\mathrm{ker}_0(R/\xi)\mathrm{ker}_0'(R/\xi) + \mathrm{kei}_0(R/\xi)\mathrm{kei}_0'(R/\xi)}{\mathrm{ker}_0^2(R/\xi) + \mathrm{kei}_0^2(R/\xi)}, \quad (13)$$

which in the planar limit

$$R/\xi \to \infty \text{ yields } \psi' \to -\frac{1}{\sqrt{2}}. \quad (14)$$

The solution is shown as a function of the shifted coordinate $\chi = \rho - R/\xi$ for different values of the parameter R/ξ in Fig. 1. The inset shows the variation of the initial derivative with inverse inclusion radius. The minimal free energy is now obtained obtained by inserting ψ' from Eq. (13) into Eq. (12) as

$$F(R/\xi) = 2\sqrt{2}\pi F_0\frac{R}{\xi}(a_2^2 + a_3^2)\left[\mathrm{ker}_0(R/\xi)(\mathrm{ker}_1(R/\xi) - \mathrm{kei}_1(R/\xi)) + \mathrm{kei}_0(R/\xi)(\mathrm{ker}_1(R/\xi) + \mathrm{kei}_1(R/\xi))\right] \approx F_0 2\pi\sqrt{2}R/\xi. \quad (15)$$